Clinical evaluation of the efficacy of methylnaltrexone in resolving constipation induced by different opioid subtypes combined with laboratory analysis of immunomodulatory and antiangiogenic effects of methylnaltrexone

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To compare the efficacy of a fixed dose of SC methylnaltrexone to induce laxation in patients receiving palliative care with constipation due to either fentanyl, oxycodone or morphine sulphate (opioids with different mechanisms of action). Secondary...

Ethical review	Approved WMO
Status	Completed
Health condition type	Gastrointestinal motility and defaecation conditions
Study type	Observational invasive

Summary

ID

NL-OMON39494

Source
ToetsingOnline

Brief title
Methylnaltrexone for opioid induced constipation

Condition

- Gastrointestinal motility and defaecation conditions

Synonym
constipation

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Fonds Nuts Ohra

Intervention

Keyword: constipation, methylnaltrexone, opioid

Outcome measures

Primary outcome

The proportion of subjects that has a rescue-free laxation response within 4

hours after at least 2 of the first 4 doses (the first week of treatment).

Secondary outcome

- time to first laxation

- laxation within 4 hours after the first dose of study drug

- laxation within 4 or 24 hours after each dose

- laxation within 4 hours after at least 4 of the maximum 7 doses

- number of laxations per week

- change in BFI score between day 0 and 14

Other study parameters:

1. Changes in leukocyte subsets and serum cytokine levels. The frequency of the

following leukocyte subsets will be evaluated: T-, B-, NK-cells,

monocytes/macrophages, MDSC, DC subsets, neutrophilic granulocytes, and

regulatory cell populations (invariant NKT cells, CD4+CD25+FOXP3+ regulatory T

cells). Serum cytokine levels will include e.g. IFN-γ, IL-2, IL-4, IL-5, IL-6,

IL-10, IL-17 and TNF-α.

2. Determination of the angiogenic profile by determination of angiogenic

factor blood concentrations and the systemic levels of endothelial progenitor

cells.

3. Determination of the angiogenic potential of blood on in vitro endothelial

cell proliferation assays before and during treatment with methylnaltrexone (in

a subgroup of patients, maximally n = 10 per group).

Study description

Background summary

Methylnaltrexone for the treatment of opioid-induced constipation in the setting of palliative or hospice care, is significantly more effective than placebo. However, in both the randomized and the open-label phase of the multi center trial showing this favorable outcome, the drug produced rescue-free laxation in only about half of the patients. There may be several reasons for this result, since constipation in palliative care patients often has multiple simultaneously occurring causes.
Assuming that constipation of the non-responders is still opioid-induced, one of the possible reasons for not responding to methylnaltrexone could be that central actions of opioids contribute to constipation by reducing motility of the intestines through direct actions in the spinal dorsal horn. However, as methylnaltrexone is a μ-receptor antagonist and not all opioids are solely μ-receptor agonists another reason may well be that successful laxation is determined by the receptor-profile of the specific opioid the patient is using.
Opioids do not only influence bowel functioning, but also immune system functioning and angiogenesis. Methylnaltrexone possibly antagonizes these changes, therefore this study will also investigate the influence of methylnaltrexone on immunologic and angiogenic parameters.

Study objective

To compare the efficacy of a fixed dose of SC methylnaltrexone to induce laxation in patients receiving palliative care with constipation due to either fentanyl, oxycodone or morphine sulphate (opioids with different mechanisms of action). Secondary objectives are to evaluate the influence of methylnaltrexone on immunologic function and angiogenic activity of patients on opioid

treatment.

Study design

A prospective observational study with an exploratory part on immunologic and angiogenic functioning. Study patients are divided over three groups depending on the type of opioid they use, being either morphine sulphate (n=78), oxycodon (n=78) or fentanyl (n=39). All patients will receive methylnaltrexone 8 mg, 12 mg or 0.15 mg/kg (depending on their weight) every other day for 14 days. From patients participating in the exploratory part of the study 58 ml of blood will be drawn on days 0, 1, 14 and 42.

Study burden and risks

Methylnaltrexone has been registered for this indication. Therefore participation in this trial does not cause any extra risks. Common side effects of methylnaltrexone are abdominal pain, nausea, flatulence and diarrhea. Other possible side effects are dizziness and local reactions at the injection site such as erythema, pruritus and edema. Rare side effects that are mentioned are abdominal cramps, increased body temperature, GI perforation, muscle spasm and syncope.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Age >= 18 years
2. Receiving supportive care
3. Life expectancy >= 2 weeks
4. Able to give informed consent
5. Receiving opioid treatment with either morphine sulphate, oxycodone or fentanyl
6. Opioid treatment, both
a) On a regular schedule (not just as needed or rescue doses) for the control of pain or dyspnea for at least 2 weeks before the first dose of methylnaltrexone, and
b) On a stable opioid regimen for at least 3 days before the first dose of methylnaltrexone. This is defined as no dose reduction of >= 50%, dose increases are permitted.
7. If a subject uses a combination of short- and long-acting (including continuous administration) opioids, the short-acting opioid should preferably be of the same type as the long-acting opioid. If the subject uses a different type of short-acting opioid than the long-acting opioid, the subject is allowed to enter the study if he/she has used this short-acting opioid <= 2 times a day in the past three days.
8. Has diagnosis of constipation, defined as either
a) < 3 bowel movements during the previous week by history and no clinically notable laxation* in the 24 hours before the first dose of methylnaltrexone, or
b) No clinically notable laxation* in the 48 hours before the first dose of methylnaltrexone.
9. Constipation is defined as opioid induced, determined by investigator
10. On stable laxative regimen for >= 3 days before the first dose of methylnaltrexone. This is defined as at least one type of laxative in an adequate dosing regimen, (e.g. macrogol 2 packets daily, magnesium(hydr)oxide 500 mg three times daily, bisacodyl 10 mg daily or sennoside A+B 10 ml daily) or at least two types of laxatives in a suboptimal dose with patient characteristics hampering optimal treatment.
11. If the subject is a woman with presumed child bearing potential; negative urine pregnancy test at screening
12. Surgically sterile or agrees to use a medically acceptable method of birth control or practice sexual abstinence for the duration of the methylnaltrexone treatment and the following 15 days. ~;* including laxation after rescue laxative or enema
~ not necessary for postmenopausal women

Exclusion criteria

1. Previous treatment with methylnaltrexone while using the same opioid subtype

2. Known or suspected mechanical gastrointestinal obstruction
3. Presence of an other cause of bowel dysfunction that is considered to be a major contribution to the constipation according to investigator
4. Presence of a peritoneal catheter for intraperitoneal chemotherapy or dialysis
5. Clinically relevant active diverticular disease
6. History of bowel surgery within 10 days before first dose of methylnaltrexone
7. Fecal ostomy, except for patients who*s defecation pattern was comparable to patients without a fecal ostomy before start of this constipation episode.
8. Use of vinca alkaloids within previous 4 months
9. Body weight <38 kg
10. Renal failure defined as EGFR <30 ml/min per 1.73m2 or requires dialysis.
11. Known or suspected allergy to methylnaltrexone or similar compounds (e.g. naltrexone or naloxone)
12. Participation in a study with investigational products within 30 days before first dose of methylnaltrexone.
13. Pregnant or nursing
14. Clinically important abnormalities that may interfere with participation or compliance to the study, determined by investigator ;Additional exclusion criteria for the immunologic and angiogenic analysis part of the study:
15. Chemotherapy or treatment with tyrosine kinase inhibitor during 4 weeks before inclusion or treatment scheduled during participation in this study.
16. Treatment with high dose corticosteroids during 2 weeks before inclusion in this study. This is defined as the equivalent of 30 mg of prednisone per day for >= 2 consecutive days.

Study design

Design

Study phase:	4
Study type:	Observational invasive
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	25-07-2012
Enrollment:	195
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Relistor
Generic name:	methylnaltrexone
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	29-05-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-07-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-11-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-02-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-05-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-06-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-02-2014
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-03-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2012-000850-75-NL
CCMO	NL39951.029.12